UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,676	10/17/2003	John M. Yanni	2394 US	2568

26356 7590 11/16/2006

ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

EXAMINER	
SINGH, ANOOP KUMAR	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/688,676	YANNI ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 5-22 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 5-22 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendments filed on September 8, 2006, has been received and entered. Claims 8 and 17 have been amended, while claims 1-4 have been cancelled. Claims 5-22 are pending.

Maintained-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-22 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 5 and 14 encompass a method of treating dry eye in a postmenopausal patient by incorporating nucleic acid encoding 15-lipoxygenase-1, -2 gene products into an *in situ* ocular cell under condition permissive for uptake of nucleic acid such that nucleic acid is expressed and dry eye condition is treated. The dependent claims 6 and 15 recite nucleic acid encoding the gene product.

Claims 7-8 and 16-17 limit the cells of claim 6 and 15 respectively to include conjunctiva or corneal epithelial cells that is debrided under conditions permissive for the uptake of nucleic acid such that nucleic acid is expressed and patient is treated. Claims 9-13 and 18-22 encompass viral vector and plasmid for delivering the gene to be expressed in ocular cell as claimed. The subsequent claims limit transgene in either retrovirus or adeno or adeno-associated virus.

The application as filed is not enabling for the invention because art of targeted gene therapy in eye for the treatment of a specific condition is unpredictable as has been recognized by the art of skill and therefore require undue experimentation. As will be shown below, these broad aspects as well as limitations were not enabled for the claimed invention at the time of filing of this application because neither the specification nor the art of record taught sufficient guidance to practice the claimed invention commensurate with the scope of the claim.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working example are not disclosed in the specification, therefore enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in enablement rejections are those raised in the art by artisan of expertise.

The aspects considered broad are: the breadth of subject population encompassing any postmenopausal patient, the breadth of any vector that could be used for treating dry eye condition subsequently limiting to few, any method of administration to affect eye, the increase of expression of transgene in many ocular

cells then limiting to conjunctival or corneal epithelial cell and transgene not operably linked to expression control elements a critical limitation not described in claims.

The invention (claims 5-22) encompasses a method of treating dry eye condition by incorporating into an ocular cell via any route nucleic acid encoding 15-lipoxygenase-1, -2 such that transgene is expressed and the dry eye condition of postmenopausal patient is treated.

The Nature of such Invention is within the broad genera of gene therapy, and gene therapy is not generally enabling of Applicant's invention due to problems with, *inter alia*, targeting and expression of transgenes at therapeutically effective level by any route in any specific tissue for the treatment of specific condition. For purposes to be shown in the state of the prior art, the question of lack of enablement is discussed.

The specification broadly discloses the need for composition and treatment for dry eye condition particularly in postmenopausal women (pp. 2). The invention is based in part on the discovery that mucin reside in the apical and sub apical corneal epithelium which is secreted via cornea apical, sub apical cells and conjunctival epithelium of human eye (pp 4-5). Page-5 describes different part of the body that produces and secretes mucin and it briefly lists agents that increase mucin and/or tear production. Page-7 broadly tracks claim language. The present inventor discloses that ocular surface epithelium of postmenopausal women lack 15-lipoxygenase. This is required for the synthesis of 15(s)-HETE, which in turn stimulates the production of MUC-1 mucin (pp 8). Pages 9-13 broadly discuss role of lipoxygenase, *in situ* ocular cells, method and type of vector and its use, target ocular cells and permissive condition of nucleic acid uptake for the treatment of dry eye condition.

However, such broad disclosure does not demonstrate the information required by the Artisan to reasonably predict that any transgene can be expressed in ocular cells of human at minimum effective levels for therapeutic response. The specification does not provide any specific guidance for expressing the nucleic acid Seq ID no 1 or 3 at therapeutic effective level in ocular cells of postmenopausal women.

In fact, the art of gene therapy at the time of the filing of this application was unpredictable wherein any gene was expressed in an individual suffering from dry eye

or other ocular disease. Furthermore, the state of the prior art effectively summarized by the references of Verma and Somia (1997) Nature 389:239-242 and Pfeifer and Verma (2001) Annual Review of Genomics and Human Genetics.2: 177-211 describes progress made in developing new vectors and also suggest vector targeting *in vivo* to be unpredictable and inefficient. Verma et al., reviews various vectors known in the art for use in gene therapy and problems associated with each implying that at the time of claimed invention resolution to vector targeting had not been achieved in the art (Verma et al., 1997; Pfeifer et al., 2001; entire article). They highlight some advantages of using retroviral and adeno-associated viral vector in gene therapy but also acknowledge a greater level of skepticism in using these vectors in human (Pfeifer et al., 2001; abstract). It is noted by the authors that more efficient and safe vectors are required to deliver gene to the target cell for therapeutic effective level of gene expression (Pfeifer and Verma 2001, Annual Review of Genomics and Human Genetics.2: 177-211, pp 201).

Given this lack of reasonable predictability in Applicant's specification and the art, the Artisan would require a large amount of information from Applicant's examples to provide the guidance to provide reasonable predictability.

Applicant's examples only describe that 15-Lipoxygenase is expressed in eye. Specifically, Example 1 demonstrates that RP-HPLC analyses of conjunctiva samples showing moderate activity in seven out of 21 samples. The specification discloses four samples that were positive for 15- LO activity for RT-PCR analyses. The results showed only one out of four positive for 15-LO-1 and 1 sample positive for both iso-enzyme. It is emphasized that neither art nor instant specification explicitly teach that lack of 15-lipoxygenase-1,-2 in postmenopausal patients result in dry eye condition. The specification on page 8, lines 6-8 states, "... present invention stems from the discovery that the ocular surface epithelium of postmenopausal women **may** lack 15-lipoxygenase (15-LO) (pp 8)" suggesting it was just a hypothesis. The art of record only implies potential benefit of supplementing 15-lipoxygenase for the treatment of dry eye condition, however, such an implied statement does not provide specific guidance to practice an unpredictable invention. It is also not clear from the specification whether

the example disclosed in the specification uses tissues derived from *ex-vivo* or *in vivo* experiment. In addition, Applicants do not provide any disclosure on type of vector and method of delivering that vector to express transgene in the subject. Furthermore, it is not enough to reasonably predict that the transgene can be expressed using vectors via any route of administration at reasonable level for appropriate time duration at appropriate cells of eye for the treatment of dry eye conditions in human. Because of the art, as shown above, does not disclose that postmenopausal women lack 15-lipoxygenase-1, -2 activity in eye and it is also not apparent how the claimed vectors would be effective in any postmenopausal patients. Artisan could not predict, in the absence of proof to the contrary, that such applications would be efficacious in therapeutic treatment. The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to (1) how an artisan of skill would have practiced the claimed method in postmenopausal patient (ii) the claimed method would have resulted in expression of 15-lipoxygenase-1,-2 in amount sufficient to treat the dry eye conditions by administering transgenes via any route in "postmenopausal patient". An artisan would have to carry out extensive experimentation to make use the invention, and such experimentation would have been undue because of the art of gene therapy and gene delivery *in vivo* is unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

Next, the claims (9-13 and 18-22) recite vectors and plasmid for delivering transgene in ocular cells. It is noted that Stechschulte, et al. (2001) Investigative Ophthalmology & Visual Science: 42(9): 1975-1979 (IDS), teach efficacy and safety of naked plasmid gene therapy to the corneal stroma and epithelium of mice. However, authors also conclude that how broadly these technique would be applied could be determined only by ongoing work in the art (pp 1978, last paragraph). Thus, while art of record teaches administration of naked DNA to cornea in ocular disease of mice, these findings cannot be extrapolated for the treatment of dry eye condition of a postmenopausal patient as discussed in previous office action. The specification merely provides a general description that is not sufficient to provide enabling support because

claimed therapy method cannot be actually reduced to practice until the skilled artisan is provided by sufficient guidance to how much and how long the transgene expression would be required to attain therapeutic response in postmenopausal patients. These methods would have required undue experimentation because neither the specification nor the art of record teaches specific guidance for treating dry eye condition by over expressing 15-lopoxygenase-1, -2 in postmenopausal patients.

Cuthbertson (US patent no, 6204251, dated 3/20/2001) provides a general method of incorporating an exogenous transgene in eye. It is noted that Cuthbertson et al disclose a replication-incompetent recombinant adenoviral vector that delivered a beta-galactosidase marker gene. It is noted that Cuthbertson shows positive staining of the majority of cells lining the posterior surface of the cornea in the animals that received the viral vectors as compared to control animals that received vehicle alone (Figure 2 A and 2B, Example 2, col. 10, lines 5-14). However, it is emphasized that data of Cuthbertson is a general method for effecting expression of an exogenous gene in ocular cells which is not enabling disclosure for treating a disease and cannot be extrapolated to a very specific treatment method for a specific condition by delivering a specific nucleic acid as claimed in instant application. In fact, numerous factors complicate the gene delivery and therapy art that could not have been overcome by routine experimentation. These include, the fate of DNA vector itself, volume of distribution, rate of clearance in tissue, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of RNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ significantly based on the vector used and the protein being produced (Goodman & Gilman's The Pharmacological basis of Therapeutics, McGraw-Hill, New York, NY. pp 77-101). Therefore, an artisan would have to carry out extensive experimentation to make use the invention, and such experimentation would have been undue because of the art of treating a specific condition such as dry eye in any postmenopausal subject using plurality of vector is

unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced for the treatment of dry eye condition in a postmenopausal patient.

Next, Behrens, et al. (2002) Investigative Ophthalmology & Visual Science: 43(4): 968-977, teaches *in vivo* efficacy and safety of ophthalmic topical treatment of a retroviral vector bearing an antiproliferative dominant negative mutant cyclin G1 (dnG1) construct in corneal haze after phototherapeutic keratectomy (PTK) in rabbit. In addition, Kamata et al., (Mol Ther. 2001, 4(4): 307-312) teach adenovirus-mediated transduction efficiency in mouse eyes using an adenoviral vector expressing *E. coli* β-galactosidase. It is emphasized that they failed to transfer gene onto the cornea by administering drops of a solution containing adenovirus AxCALacZ. However, direct injection of adenovirus expressing AxCALacZ into the anterior chamber resulted in Lac Z expression in the inner layer of cornea (pp 308, 3rd paragraph).

Martin, et al. (2002) Methods: 267-275, evinces an optimistic outlook for the treatment of ocular disorder using adneo-associated viral vector (AAVV), but also acknowledges that the art is not yet generally enabling for humans (pp 268 3rd paragraph). It is noted that Martin et al (Methods 2002: 267-275) emphasize that efficiency of transfection of specific cell types of eye are dependent on a number of variables including the site of injection, the AAV serotype and titer and the amount of DNA (pp 268-269). The specification does not provide any specific guidance to address these issues.

Furthermore, in the instant case, the results of Cuthbertson or Stechschulte, or Behrens or Kamata or Martin cannot be predictive of treating deficiency of 15-lipoxygenase in treating dry eye condition of postmenopausal patient because above described genes are used in animal model for different cause, diseases and cannot be extrapolated to treating dry eye condition in postmenopausal women. This fact is supported by the fact that no appropriate animal model exists for dry eye condition. In fact, recently Barabino et al., (Investigative Ophthalmology & Visual Science. 2004,45(6): 1641-1646) describe, "all the existing animal models of dry eye mimic different pathogenic mechanisms of Dry eye syndrome, or keratoconjunctivitis sicca

(KCS) and at the moment none of them seems to mirror precisely the complexity and chronicity of this frequent and debilitating condition" (pp1645; Conclusion). This clearly establishes the unpredictability of the animal models currently being used for evaluating therapeutics effective against dry eye. Therefore, a general method of expressing transgene in any other disease model cannot be directly extrapolated to treatment of dry eye conditions in humans. The specification also does not provide any guidance as to how studies in animal model can be extrapolated to human situations. Furthermore, It is also noted that, the specification does not teach whether viral vectors or plasmid can be used effectively in administering transgene either via any route in postmenopausal patients. In addition, prior art at the time of filing of this application as described before did not provide any convincing guidance in this regard either.

In reviewing the above-discussed problem, it is evident that the artisan would require, making and/or using a new invention in the field. A showing that enough of 15-lipoxygenase-1, -2 reaches the target cell, enough nucleic acid is incorporated into ocular cells, that such nucleic acid is properly incorporated into such cells as DNA, enough mRNA is produced therefrom, and enough protein is produced and 15-lipoxygenase-1, -2 have an effect on the ocular cells and such effect is enough of an effect for a long enough period of time. Alternatively, direct example of such effect of 15-lipoxygenase-1, -2 would overcome this showing specifically for 15-lipoxygenase-1, -2 if these transgenes are included in the vector they must have met the requirement above.

The cited arts clearly indicate an unpredictable status of the gene therapy art pertaining to treatment of dry eye condition. Although, specific vectors, promoters, genes, and route of administration might be or may have been effective for treatment of specific disease providing specific therapeutic effect. Gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest, which results in a therapeutic effect.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions. The specification and prior art do not teach a method of *in vivo*

delivery of a gene such that it is expressed at therapeutic effective level for desired duration in the eye of a postmenopausal women suffering from dry eye condition. An artisan of skill would have required undue experimentation to develop/design a suitable vector and practice the method as claimed because the art of gene therapy, vector design and *in vivo* delivery and treatment of dry eye condition in general by gene delivery *in vivo* was unpredictable at the time of filing of this application as supported by the observations in the art record.

Response to Arguments

Applicant arguments filed on 09/08/2006 have been fully considered but they are not persuasive. Applicant in their argument on page 5 state that the action's main objection seems to stem from the use of prophetic example. Applicants further assert that majority of the action position relate to the assertion that there is no reasonable predictability of instant type of gene therapy. Applicants also assert that other factors are largely minimized for the purpose of *Wand analysis*. Applicants also cite references of Curtis et al and Pfeifer et al to argue that art of gene therapy has progressed rapidly between 2001 and 2003.

In response, it is emphasized that the intent of the cited reverences are not to show that a nucleic acid can never be delivered at a site or to an organ for a therapeutic response. Examine has cited references of Pfeifer et al and Verma et al to describe the state of gene therapy at the time of filing of this application which indicated that resolution of vector for gene targeting in the treatment of any condition *in vivo* was not predictable. Furthermore, contrary to applicants argument, Examiner has supported his arguments with references of Martin, Behrens, Kamata that describes the advancement in the gene therapy art. However, as stated in this and previous office action, the real issue is not whether 15-lipoxgenase-1, -2 could be delivered in eye by various vector as generally argued by the applicants, rather issue at hand is whether enough of protein is made for prolonged period of time for any therapeutic response (see page 12, paragraph 1 of office action dated 3/8/2006). Prior art teaches that numerous factors

complicate the gene therapy art that could not have been overcome by routine experimentation. These include, the fate of DNA vector itself, volume of distribution, rate of clearance in tissue, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of RNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ significantly based on the vector used and the protein being produced (Goodman & Gilman's The Pharmacological basis of Therapeutics, McGraw-Hill, New York, NY. pp 77-101, art of record; Supra). Even for the sake of argument, if one assumes that transgene is delivered to ocular cell *in vivo* using any vector or as naked DNA, it does not provide any evidence that enough of protein is being made at the desired site for appropriate duration in any subject to elicit any pharmacological response as discussed before. Furthermore, Examiner disagrees with Applicants assertion and emphasize that several of Wand factors determinative of enablement rejection were considered in previous office action dated 03/08/2006. The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors were analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled. For instance, the breadth of the claims and the nature of the invention is described on page 4, paragraph 4, bridging to page 5 paragraph 1; the state of the art of gene therapy on page 5 last paragraph to page 6 paragraph 1; the level of predictability in the art on pages 7-10; the amount of direction and guidance provided by Applicant, page 5, paragraph 2; and the existence of working examples on page 6, last paragraph bridging to page 7, first paragraph; and The quantity of experimentation needed to make and/or use the invention, page 12, paragraph 1). On page 6, applicants argue that safety issue raised by the Examiner fall

within the province of the Food and Drug Administration. In response, it is it is emphasized that Examiner had no intention to raise any toxicity or safety issue arising from using different vectors. The discussion is merely intended to address problems that are associated with vector design that differs significantly based on the vector used and the protein being produced (supra). It is noted that neither prior art nor specification provides any specific guidance that delivering transgene by any one of the claimed vector/plasmid that would result in expression of 15-lipooxgenase-1 and-2 in enough quantity for appropriate duration to elicit any pharmacological response. An artisan would have to make a new invention in the field to determine the vector, titer and route that would result in appropriate expression for desired duration in the eye of any post menopausal women suffering form dry eye.

On page 7, Applicants argue that office action distinguishes Cuthbertson on the grounds that effecting expression in ocular cells is not enabling to treat a disease and that it only teach gene therapy method for nonhuman animal only. Applicants assert that action is contradictory to the teaching of Cuthbertson that describes a method for treating ocular disease in an *in situ* ocular cell that is *in vivo*. Applicants also argue that gene therapy was a known method of treatment and that its use was believed to be effective at the time of filing of this application (see page 7 paragraph 2).

In response, it is emphasized that Examiner has only stated the previously expressed position of applicants in reply to office action stating "Cuthbertson describes general methods for effecting expression of an exogenous gene in ocular cells" (see argument filed on 1/17/2006, page 6, paragraph 2, lines 9-10). As state before and reiterated here, the patentability of each patent application is examined in view of its own disclosure and merits depending on what is claimed. Cuthbertson describes a general method for treating any ocular disorder by effecting expression of an exogenous gene in ocular cells. This cannot be an enabling disclosure for treating a specific disease as recited in the instant case and the teaching of Cuthbertson cannot be extrapolated to a very specific treatment method for a specific condition by delivering a specific nucleic acid as claimed in instant application for the reasons of the record. For instance, claims 5-22 are directed to delivering specific nucleic acid encoding protein as

set forth in specific sequence identification number that would have different fate, volume of distribution, rate of clearance in tissue, the *in vivo* consequences of altered gene expression and protein function, fraction of vector comprising seq ID 1 and 3 taken up by the target cell population, the trafficking of the genetic material within cellular organelles and the amount and stability of the protein produced. These factors will be different depending upon the method and site of administration and would have different pharmacological response. The instant specification merely provides a general description that is not sufficient to provide enabling support because claimed therapy method cannot be actually reduced to practice until the skilled artisan is provided by sufficient guidance with each one of those previously discussed elements to attain therapeutic response in postmenopausal patients. These methods would have required undue experimentation because neither specification nor art of record provide any specific guidance to a method of treating dry eye condition by over expressing 15-lipoxygenase-1, -2 in postmenopausal patients. In absence of any such explicit teaching, a skilled artisan would have to determine the status of 15-LO-1, -2 in postmenopausal women.

On page 8, Applicants argue that Behrens and Kamata have described successful in vivo gene transfer by topical treatment and injection

In response, it is again emphasized that the issue is not whether one could deliver transgene in eye rather issue is whether expression of 15-lipoxygenase-1, -2 could be achieved at sustained level in any subject for appropriate time for any therapeutic response. As stated in previous office action, Examiner had summarized his arguments with these three references in conjunction with the teaching of Barabino et al. It is noted that applicants have not presented any argument in this regard. While analyzing the issue of predictability, one cannot solely rely on theoretical basis of beneficial effects of any gene in a therapeutic method. The fact that Barabino et al., (Investigative Ophthalmology & Visual Science. 2004,45(6): 1641-1646) describe, "all the existing animal models of dry eye mimic different pathogenic mechanisms of Dry eye syndrome, or keratoconjunctivitis sicca (KCS) and at the moment none of them seems to mirror precisely the complexity and chronicity of this frequent and debilitating

condition" (pp1645; Conclusion; supra). Barabino et al describes that pathogenic mechanism of dry eye could be multi factorial and could be due to lacrimal inflammation, interruption of neuronal stimulation for tear secretion, defect in membrane and secretory mucin expression, meibomain gland dysfunction. Barabino et al also describe that studies incorporating both intrinsic factors such as immune, endocrine and neuronal and extrinsic factor would provide some advancement in the field of dry eye (see conclusions). It is emphasized that Barabino noted, "there are many variables that influence hormonal effects on lacrimal glands of animals including their species, strain, gender and age to name few". Therefore, in view of above discussion it is apparent that Examiner's arguments that results of Cuthbertson or Stechschulte, or Behrens or Kamata or Martin cannot be predictive of treating deficiency of 15-lipoxygenase-1, -2 in treating dry eye condition of postmenopausal patient is convincing particularly because genes described by Cuthbertson or Stechschulte, or Behrens or Kamata or Martin are different and they are used in different animal model for different diseases. Therefore, these cited arts couldn't be extrapolated to treating dry eye condition in postmenopausal women as different factors influenced dry eye condition and there was no single predictive animal model as supported by the teaching of Barabino et al (Investigative Ophthalmology & Visual Science. 2004,45(6): 1641-1646; art of record). Therefore, a general method of expressing transgene in any other disease model as disclosed by Cuthbertson cannot be directly extrapolated to treatment of dry eye conditions in postmenopausal women by simply delivering nucleic acid encoding SEQ ID1 or 3. The specification also does not provide any guidance as to how studies in animal models for a different disease could be can be extrapolated to human situations for the treatment of dry eye as recited in the instant invention. In summary, the specification and prior art do not teach a method of *in vivo* delivery of a gene such that it is expressed at therapeutic effective level for desired duration (emphasis added) in the eye of a postmenopausal women suffering from dry eye condition.

Withdrawn-Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8 and 17 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendment to the claims.

New-Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 5-22 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-22 of copending Application No. 10/539,093. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claims 5-22 are directed to a method of treating dry eye in a postmenopausal patient by incorporating nucleic acid into an in situ ocular cell under conditions permissive for the uptake of nucleic acid encoding protein having sequence set forth in SEQ ID NO:1, wherein nucleic acid sequence consists essentially of the sequence set forth in SEQ ID NO: 1. Claims 7-8 limit the cells to include conjunctival or corneal epithelial cells that are debrided prior to introducing said nucleic acid. Claims 9-13 recite nucleic acid is in different vectors or in a plasmid. Claims 14-22 are drawn to a method of treating dry eye in a postmenopausal patient, by incorporating nucleic acid into an in situ ocular cell under conditions permissive for the uptake of said nucleic acid, said

nucleic acid encoding a protein having the sequence set forth in SEQ ID NO:4, whereby said nucleic acid is expressed and said disease is treated wherein said nucleic acid sequence comprises the sequence set forth in SEQ ID NO:3 and said cells are conjunctival or corneal epithelial cells that are debrided prior to introducing said exogenous nucleic acid. Claims 18-22 limit nucleic acid in different vectors. While, claim 1 of '093 application is directed to a method for treating dry eye by obtaining a composition comprising SEQ ID NO:1 or SEQ ID NO:3; and administering said composition to a patient suffering from dry eye under conditions such that SEQ ID NO:1 or SEQ ID NO:3 is expressed. Claims 2 limits the composition of claim 1 to include a vector a vector comprising the sequence set forth in SEQ ID NO:1 or SEQ ID NO:3. Claims 3-4 limit the method of administration to include topical ocular drops or ointment in a pharmaceutically acceptable excipient. Claim 5 is drawn to a method of treating dry eye in a postmenopausal patient by incorporating nucleic acid into an in situ ocular cell under conditions permissive for the uptake of said nucleic acid, said nucleic acid encoding a protein having the sequence set forth in SEQ ID NO:2, whereby said nucleic acid is expressed and said disease is treated wherein said nucleic acid sequence comprises the sequence set forth in SEQ ID NO:1. Subsequent claim limit the method to include conjunctival or corneal epithelial cells that are debrided prior to introducing said exogenous nucleic acid. Claims 9-13 describe nucleic acid in different vectors. Claims 14-22 are drawn to a method of treating dry eye in a postmenopausal patient, by incorporating nucleic acid into an in situ ocular cell under conditions permissive for the uptake of said nucleic acid, said nucleic acid encoding a protein having the sequence set forth in SEQ ID NO:4, whereby said nucleic acid is expressed and said disease is treated wherein said nucleic acid sequence comprises the sequence set forth in SEQ ID NO:3 and said cells are conjunctival or corneal epithelial cells that are debrided prior to introducing said exogenous nucleic acid. Claims 18-22 limit nucleic acid in different vectors.

Conclusion

No Claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272- 0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh, Ph.D.
Examiner, AU 1632

AU 1632